that include validated threshold values that can be used to identify children at risk for delayed development or clinically significant behavioral problems (Bayley 1993; Gioia et al. 2003; Wechsler 2002). The comparison of the case child to these values is valid because the distribution of scores for children in our study are comparable to those in nationally representative population-based samples used to validate these instruments. This is how these tools are used clinically to identify children who may have neurobehavioral abnormalities.

Finally, Haighton et al. state that other etiologies could be responsible for the abnormal exam at 1 month of age. We stated this exact same point very clearly in our case report (Sathyanarayana et al. 2011). Although these other etiologies may be important in infant and child neurodevelopment, they would be confounders only if they are associated with both BPA exposure and neurodevelopment (Hernan et al. 2002).

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An Integrated Approach to the Exposome

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The editorial by Lioy and Rappaport (2011) provides a timely addition to the discussion about the exposome and exposure science. We are encouraged by the recognition of the importance of combining measurements of personal exposure with measurements of biological markers of exposure. However, rather than focusing on two approaches (i.e., top-down vs. bottom-up), we advocate a fully integrated approach to measurement of the exposome.

There are currently serious limitations in measuring internal and external exposure. It may be feasible to measure biological markers in blood or other media periodically, but such measures are not without difficulties. Recent developments in omics technology are very promising, but many of these techniques have low reproducibility between laboratories, show high intraindividual variability, and are still expensive; in addition, uncertainties remain in biological interpretation of these markers (Vineis et al. 2009). It is still often impractical to prospectively measure personal inhalation, dermal, and ingestion exposure. Such information could be collected periodically, but the scientific effort would be great and the intrusion into the subjects' lives would probably be unacceptable. Increased research effort will undoubtedly help improve measurement of both internal and external exposure. However, other sources of information exist that could contribute to constructing the exposome.

We all routinely leave traces of our exposome in everyday electronic databases or databases that could be easily constructed. For example, the goods we purchase in a supermarket are often tracked by loyalty cards, which may provide a rich source of information on food consumption and the consumer products we use. Consumption of electricity and natural gas is increasingly being logged electronically by utility companies to assist billing. These data could be used to determine use of electrical items (informative about exposure to electric and magnetic fields) and activity patterns. It is relatively straightforward to track movements of individuals using mobile phones, and these data can be used, for example, to help estimate exposure to air pollutants.

Within the next few years we will see an explosion in availability of sensors for many environmental contaminants that will be relatively cheap and easy to use and that could provide a more or less continuous log of information that can be related to exposure. These include simple sensors in the homes of subjects that continuously record information on air temperature, airborne contaminants, and other environmental factors. These sensors may provide personal exposure data or could, in combination with activity patterns and behavior, be used to reconstruct exposure profiles.

The availability of data on use and activity patterns, as well as developments in sensor and omics technology, suggests that the dichotomy in top-down and bottom-up approaches may not be appropriate, as there are other strategies that could be used to determine the exposome. In addition, the terms "top-down" and "bottom-up" may be interpreted differently, with consequent confusion of terminology. Instead, we should aim to develop a concept of the exposome that takes into account all sources of available exposure information.

The key factor in developing an integrated approach will be the articulation of clear theoretical paradigms linking exposures with disease. All of the exposure and contextual data could be used to reconstruct the exposome of individuals in an epidemiological study using appropriate models to link the data to parameters of interest in the exposome. Data on internal and external exposures, data on personal behavior, and environmental information from sensors could be used to triangulate on the exposome.

This is an extremely exciting time in exposure science, and we believe that the coming years will provide a great opportunity to make a significant leap forward in understanding the relationship between environmental exposure and disease. Maximizing the opportunities provided by various developments requires a fully integrated approach to the exposome. This approach must be based on a clear theoretical framework that incorporates measurement and modeling of external exposure, databanks on patterns of behaviors, and markers of internal exposure.

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An Integrated Approach to the Exposome: Rappaport and Lioy Respond

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We welcome the remarks of van Tongeren and Cherrie regarding our recent editorial (Lioy and Rappaport 2011) and see no particular differences in our positions. As originally conceived, the exposome concept promoted investigations of disease etiology, that is, finding unknown causes of disease (Wild 2005). This requires an untargeted study design so that important, but as yet unrecognized, exposures will not be missed (Rappaport and Smith 2010). Such untargeted designs lend themselves to omic characterization of biospecimens (of the top-down type), as has been demonstrated in recent metabolomic investigations (e.g., Wang et al. 2011). Many external measurements of exposure focus on specific chemicals or classes of agents, but van Tongeren and Cherrie offer examples of untargeted designs (e.g., mining records of household food purchases). In any case, as measurements of external phenomena become less targeted, they become more exposomic (of the bottom-up type). The real issue is to recognize the underlying reasons for estimating exposure levels. If measurements are intended to find unknown sources of disease, then they are consistent with the exposome concept. If they are intended for other purposes (e.g., dose response, risk assessment/management, source characterization), then they follow more traditional lines of exposure assessment/science. As we emphasized in our editorial (Lioy and Rappaport 2011), both approaches have merit, and a combination of the two offers particular advantages for both identifying and preventing hazardous exposures, and thereby mitigating diseases.

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Application of the Ecohealth Model to Translate Knowledge into Action in the Health Sciences

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As noted by Barkin and Schlundt (2011), addressing the public health needs of the population using evidence from biomedical research necessarily requires a wholistic approach that is both multilevel and multidisciplinary. Although there may be public health benefits, there are also important challenges when generating knowledge, at the microenvironmental level, as well as at the macroenvironmental level. This happens particularly when evidence is translated into interventions that generate benefits for all who are involved in the health process; for example, in dealing with obesity, these interventions would benefit users, the health system, food producers, and others. To complement the response to these challenges, we suggest a greater application of the ecohealth model. This model has been proposed as a new analytical model for research action based on the ecosystemic approach to human health, an approach that places health within the realm of the environment and acknowledges cause–effect interconnections between human health and humans' biophysical, social, and economic environment.

The ecohealth model stems from the generation of health knowledge and the multiple interconnections between the different components of the ecosystem. It sets forth that these interconnections are complex and interdependent and include social determinants and disparities, as well as biophysical determinants. From this perspective, scientists need to revise their models and research methods and open up to new analytical focuses and new forms of collaboration and interaction, going beyond the biophysical characteristics of systems and the scientific community itself. For many reasons, the traditional methods used in the study of the micro–macro environment have not been able to fulfill the expectations for health and welfare or those for improving sanitary conditions of populations. Thus, we need to periodically evaluate evaluations and adjust programs, interventions, and health policies.

Although traditional methods take into account the economy and the community, often at the expense of the environment (jeopardizing the possibility of a sustainable ecosystem), the ecohealth model breaks up each of its components into different categories (Hancock 1990; Lebel 2005). It confers equal importance to environmental management, economic factors, and the community's aspirations, and it places human health at the center of the intersection of these three elements. In this sense, the ecohealth model itself is part of the sustainable development process, and its fundamental premise is to be inclusive. Interventions and health programs based on evidence generated under the ecohealth model should be more cost-effective than many medical treatments or traditional healthcare interventions. This analytical model and its methodological research approach involve three participating groups: researchers and other specialists; community members, such as common citizens, businessmen, farmers, fishermen, and miners; and decision makers in health interventions. Besides the need for the participation of these three groups, the ecohealth model is based on three methodological pillars: transdisciplinarity, participation and equity.

- Transdisciplinarity implies a multilevel and translevel vision, with a broad scope and collaboration in the study of health determinants and conditions related to the ecosystem.
- Participation intends to achieve consensus on the definition of the study's objective among scientists, community members, and decision makers, both between and within groups.
- Equity includes the analysis of the roles of men and women and their different degrees of influence in decisions on access to and use of financial resources, as well as equity in benefits and rewards for all of those involved in a concrete health problem.

Each of these pillars generates, to a great extent, conditions for a more effective and